

# IL-1 and its role in osteoarthritis

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## Abstract

Given the high and rising figures of people with osteoarthritis, knowledge of new factors defining course and evolution of the disease are important, when considering new pharmacological targets. IL-1 is a very important cytokine in the early steps of osteoarthritis, giving the high sensitivity of the chondrocytes to this cytokine, and it can be considered the bridge permitting the dialogue between the different structures of the articulation, in such a way that the cartilage is not the only tissue affected in OA. IL-1 increases the destruction of the extracellular matrix of the cartilage increasing the collagenolytic activity of metalloproteases, increasing activity of nitric oxide ON, which can induce apoptosis of chondrocytes. Interestingly, IL-1 further induces changes in the homeostasis of the cartilage, lessening activity of growth factors, such as TGF-beta.

**Key words:** IL-1 - osteoarthritis - MMP - nitric oxide - cartilage homeostasis.



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## Osteoarthritis impact and magnitude

Osteoarthritis (OA) is the most common joint disease and it is ranked among the most frequent and symptomatic causing health-problems disease for middle-aged people as well as in the elderly. The main characteristic of OA is an imbalance between chondrocyte anabolic and catabolic activities, as it is described in the section of cartilage homeostasis.

The implications of this burden are poor quality of life, restrictions in daily activities and progressive disability (van der Waal JM et al, 2005).

The biggest condition causing disability is osteoarthritis, and altogether with joint pain in older people—will be an increasingly important public health concern in the elderly.

## Osteoarthritis pathophysiology

Degenerative articular disease is best characterized by a loss of the equilibrium or changes in the cartilage homeostasis, and it means further degradation of the molecules of the cartilage matrix.

The loss of proteoglycans and another macromolecules from cartilage yields in a progressive tissue destruction, causing deterioration of the smooth cartilage surface (Pujol JP, 1998).

The extracellular matrix represents the microenvironment for the chondrocytes, in addition to its mechanical importance.

### Loss of cartilage homeostasis

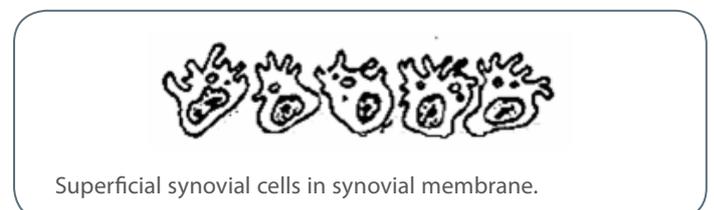
During joint disease, the normal equilibrium in cartilage is disrupted and the rate of loss of collagens and proteoglycans from the matrix clearly exceed the rate of deposition of newly synthesized molecules, resulting in cartilage damage (Goldring MB & Marcu KB, 2009)

### Synovitis in osteoarthritis

Synovial inflammation occurs early in OA and can be subclinical, as arthroscopic studies suggest that localized proliferative and inflammatory changes of the synovium occur in up to 50% of OA patients (many of whom do not appear to have active inflammation) (Krasnokutsky S et al, 2007).



Extracellular matrix of the cartilage.



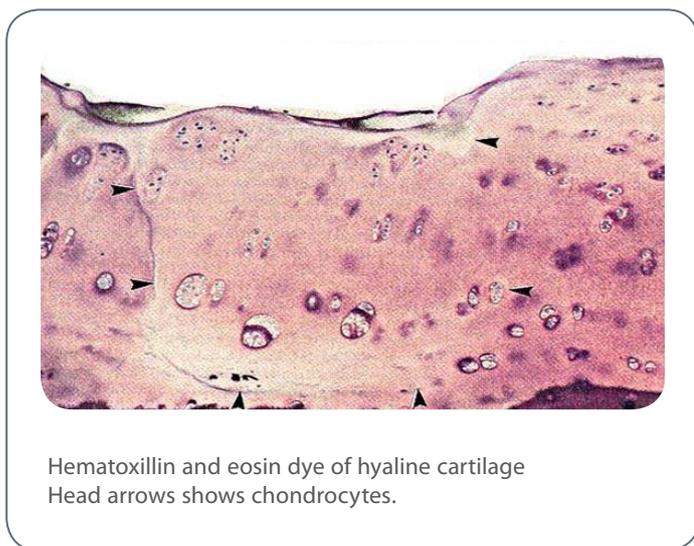
Superficial synovial cells in synovial membrane.

The synovium produces some of the chemokines and metalloproteinases that degrade cartilage, even though the chondrocytes produce mostly of these destructive molecules. This picture is attributed to the presence of IL-1 in the synoviocytes.

Synovitis plays a established role in the progression of osteoarthritis and the overproduction of cytokines specially interleukin 1 and growth factors from the inflamed synovium can influence the production of degradative enzymes such as matrix metalloproteinases causing the destruction of cartilage (Bondeson J et al, 2006)

## Chondrocyte role in cartilage maintenance

The chondrocytes are the only cell type found in cartilage and it regulates the maintenance of the cartilage extracellular matrix.



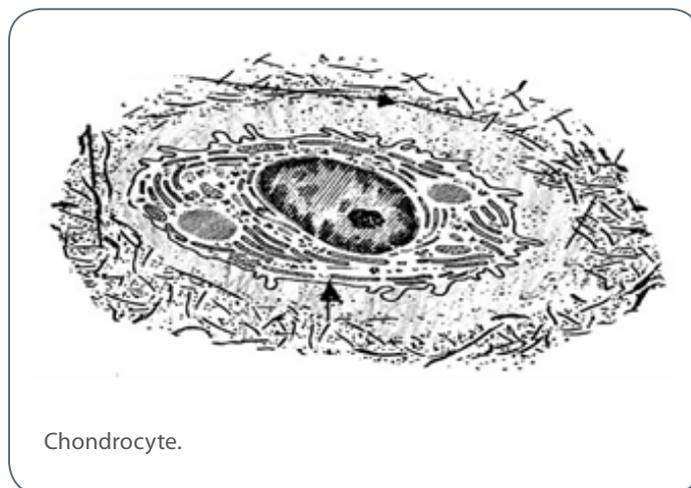
Hematoxylin and eosin dye of hyaline cartilage  
Head arrows shows chondrocytes.

The maintenance of articular cartilage integrity requires a delicate balance between anabolic process (synthesis) and anabolic process (degradation). In this delicate balance it is well known that cytokin IL-1 increases the degradation of proteoglycans and collagens.

### Cartilage homeostasis

The adult articular cartilage shows a slow tissue turnover. In this turnover, new optimal tissue bearing biomechanical stress is built and defective tissue is removed. Thus, one of the most important issues in osteoarthritis research is to understand the adequate homeostasis of catabolic and anabolic factors in articular cartilage (Aigner T et al, 2006).

Whereas the matrix is the functional component of the articular cartilage, the chondrocytes as the cell population of the



Chondrocyte.

cartilage are responsible for the homeostasis of this tissue. In normal conditions, each chondrocyte interacts with this pericellular matrix in order to keep their cellular phenotype stable. In that way chondrocytes are responsible for maintaining in a low-turnover state the unique composition and organization of the matrix.

A big deal of research *in vitro* and *in vivo* in the past two decades confirmed that chondrocytes in hyaline cartilage respond to mechanical injury, joint instability due to genetic factors, and biological stimuli such as cytokines and growth and differentiation factors. These molecules contribute to structural changes in the surrounding cartilage matrix (Goldring MB & Marcu KB, 2009)

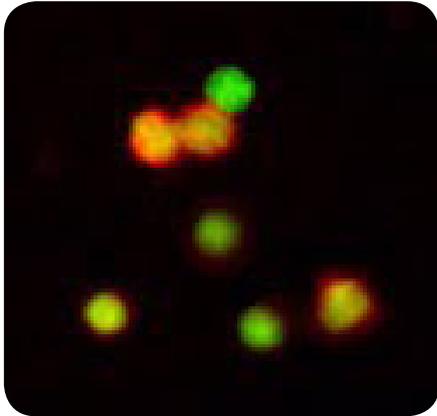
Cartilage homeostasis is the result of an equilibrated production and destruction of the ECM, but in osteoarthritis destruction predominates because of an excessive production of IL-1 induced metalloproteinases, going simultaneously with IL-1 induced alteration of the local growing factors such as TGF-beta (Pujol JP, 1998).

## Description of IL-1

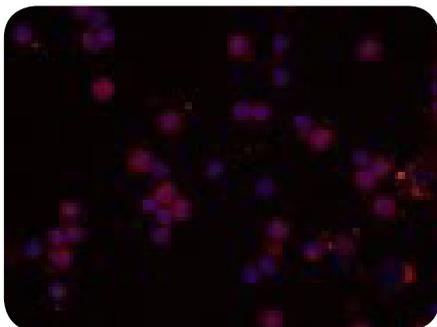
Interleukin (IL)-1 is a cytokine that plays a major role in inflammatory responses in the context of infections and immune-mediated diseases.

IL-1 is a very low molecular weight soluble peptide of the family of glycoproteins, produced and secreted in an inactive form, called proIL-1. IL-1 acts in very small quantities in the order of picomoles, suggesting there exist an *in situ* mechanism acting whether in a paracrine or in an autocrine way. IL-1 has no enzymatic activity (Mathieu P, 1999).

IL-1 refers to two different cytokines, termed IL-1alpha and IL-1beta, and they are produced from the activity of two genes. (Jacques C et al, 2006)



Interleukin-1 beta (IL-1F2) was detected in immersion fixed LPS-stimulated rat splenocytes using rat IL-1 beta antigen-purified polyclonal antibody at 5 mcg/mL for 3 hours at room temperature



Interleukin-1 alpha (IL-1F1) was detected in immersion fixed monensin human peripheral blood mononuclear cells (PBMCs), using human IL-1 alpha monoclonal antibodies at 10 mcg/ml for 3 hours at room temperature.

#### Links for images: IL-1 beta

[http://www.rndsystems.com/ihc\\_molecule\\_images.aspx?m=1629](http://www.rndsystems.com/ihc_molecule_images.aspx?m=1629)

#### IL-1 alpha

[http://www.rndsystems.com/ihc\\_molecule\\_images.aspx?m=1628](http://www.rndsystems.com/ihc_molecule_images.aspx?m=1628)

Images by kind courtesy of Tim Manning. <http://www.rndsystems.com>

## IL-1 production

It is considered three structures producing IL-1 in the articulation and triggering destruction in OA. Such an structures are, according to Mathieu (1999):

- The synovial membrane. The synthesis of IL-1 is triggered by the resorption of debris cartilage appearing in the articular cavity when there is defragmentation of proteoglycans aggregates. IL-1 present in the synovial fluid penetrates throughout the fissures of fibrillation in cartilage and then reaches the deep layers of the cartilage.
- The bone from areas directly in contact with the calcified cartilage.
- The cartilage because of the mechanical stimulation of chondrocytes.

## Levels of IL-1 in OA patients

It has been quantificated by ELISA method, employing murine antibodies to bind directly to IL-1 and rabbit antibodies marked with alkaline phosphatase to bind to the murine antibodies; the levels of IL-1 in OA, were 2,47 pg/mL at day 0, and with administration of diacerhein 100 mg daily the levels down up to 0,28 pg/mL at day 28 (Mathieu 1999).

Nevertheles this figures, there is controversy to correlate high levels with development of OA because there is high sensitivity of the chondrocytes to IL-1 and is known that OA chondrocytes are x4 times more sensitive to deleterious effects of IL-1 when compared to normal chondrocytes.

## IL-1 and its role in the pathophysiology of osteoarthritis

IL-1 stimulates the synthesis and activity of matrix metalloproteinases and other enzymes involved in cartilage destruction in rheumatoid arthritis and osteoarthritis.

Cytokines produced by the synovium and chondrocytes, especially interleukin IL-1 and tumor necrosis factor alpha (TNF- $\alpha$ ), play a significant role in the degradation of cartilage (De Isla & Stoltz JF, 2008)

The initial stages of cartilage damage are characterized by a loosening of the collagen network and a loss of proteoglycans starting in the superficial and upper middle zones. This damage spreads to deeper cartilage layers as the OA joint degeneration is going on. This type of damage is at least potentially reversible, due to the possibility of an effective increasing in the turnover of the proteoglycans in the adult tissue (Aigner T et al, 2006).

IL-1 is a potent pro-inflammatory cytokine capable of inducing chondrocytes and synovial cells to synthesize MMPs. Furthermore, IL-1 suppresses the synthesis of type II collagen and proteoglycans, and inhibits transforming growth factor- $\beta$  stimulated chondrocyte proliferation. Further the presence of IL-1 RNA and protein have been confirmed in OA joints.

IL-1 further diminishes expression in the cartilage matrix of the type II and IX collagens (Pujol JP 1998). IL-1 beta has been shown to be predominantly involved in the pathophysiology and progression of osteoarthritis.

## IL-1 and its effects in chondrocyte

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### ¿Why is IL-1 important in the pathogenesis of osteoarthritis?

Because chondrocyte is very sensitive to the effects of IL-1. Barely 1% of the receptors of IL-1 occupied in the surface of the cartilage, changes the fenotype of the chondrocyte to a catabolic one. Further the osteoarthritic chondrocyte is 3-4 times more sensitive to the effects of IL-1 (Mathieu P, 1999)

### ICE enzyme and IL-1 beta production

IL-1 gives origin to an active moiety of IL-1 through the action of Interleukin 1 converting enzyme or ICE. This enzyme produce active, mature IL-1beta.

The level of ICE has been demonstrated to be increased in OA tissues and according to investigative work of Boileau et al, it has been found to increase the production of active IL-1beta as well as IL-18. ICE is a crucial enzyme in the activation process of IL-1beta and IL-18, two important pro-inflammatory cytokines involved in the progression of OA. (Boileau C et al, 2002)

### Nitric oxide and IL-1

The production of nitric oxide (NO), which is stimulated by pro-inflammatory cytokines, is involved in cartilage catabolism and also may induce the apoptosis of chondrocytes. The NO produced by iNOS in activated chondrocytes in diseased cartilage may modulate disease progression in OA (Studer RK et al, 1999)

Nitric oxide (NO) is a pleiotropic mediator that has been shown to be intimately involved in the OA and its inhibition can induce a significant reduction in the progression of structural changes of the disease.

In another hand, OA chondrocytes have been shown to express iNOS the enzyme sintetizing ON and consequently to produce large amounts of NO, especially upon stimulation by proinflammatory cytokines (Boileau C et al, 2002)

Therefore, the oxidant molecule nitric oxide plays multiple roles with respect to chondrocytes because it promotes cartilage degradation, including inhibition of collagen and proteoglycan synthesis, it activates MMP and increased susceptibility to other oxidant injury. nitric oxide further induces oxidative injury int he chondrocyte resulting in premature senescence and apoptosis (Krasnokutsky S et al, 2007)

### Growth factors

Growth factors such as transforming growth factor beta stimulate collagens and proteoglycans synthesis by chondrocyte, and reduce the activity of IL-1 $\beta$  stimulated metalloproteases. By its capability to reduce IL-1 effects and to stimulate TGF- $\beta$  expression in cultured articular chondrocytes, drugs such as diacerein could elicitate the anabolic processes in the OA cartilage, contributing to delay the progression of the disease, and supporting structure modification in osteoarthritis (DMOAD) (De Isla NG & Stoltz JF 2008).

### Metalloproteases

In OA, synthesis of the enzymes called metalloproteases (MMPs) is greatly enhanced and the available inhibitors (tissue inhibitors of MMP or TIMPs) are overwhelmed, resulting in net degradation of cartilage.

In OA, these degradative enzymes are produced primarily by chondrocytes due to inductive stimuli, including a wide variety of stimules such as mechanical stress, injury with destabilization, cell-matrix interactions, oxidative stress, and changes in growth factor responses (such as TGF- $\beta$ ) during the aging process (Goldring MB & Marcu KB, 2009).

### Ways to demonstrate IL-1 is elevated in OA

There is recent research with imaging techniques of magnetic resonance in which significant correlation between IL-1 $\beta$  ( $r = 0.48, P < 0.05$ ) and fractional anisotropy of the magnetic resonance and inverse correlations between planar anisotropy of the magnetic resonance and IL-1 $\beta$  and soluble intercelular adhesion molecule (sICAM) ( $r = 0.48, P < 0.05$  and  $r = 0.49, P < 0.05$ , respectively) were observed (Aggarwal V et al, 2009).

Mathieu (1999) describe ELISA in synovial fluid of knee OA patients, with range between 2,47 and 0,28 pg/mL.

## Pharmacological Inhibition of IL-1: usefulness as treatment in OA

Drugs such as diacerein could inhibit catabolic responses like NO synthesis as well as MMP activity but it could also increase anabolic responses like collagen type II synthesis.

Furthermore, diacerein can inhibit the binding of NF- $\kappa$ B and AP-1 transcription factors, two key factors involved in the expression of several pro-inflammatory genes by chondrocytes, such as the inducible nitric oxide synthase gene, supporting the anti-osteoarthritic effects. (De Isla NG & Stoltz JF 2008).

## Conclusions

IL-1 is a glycoprotein of very low molecular weight, acting in paracrine or autocrine pathways in the sensitive cells. Chondrocytes are very sensitive to the actions of IL-1 because with barely 1% of the receptors occupied in the surface, it turns into catabolic phenotype.

IL-1 induces synthesis of matrix metalloproteases which are the main enzymes implicated in destruction of the ECM components. Further it induces the synthesis of ON, implicated in aging and apoptosis of chondrocytes.

Homeostasis of the cartilage depends on the equilibrium between destruction and synthesis of the components of ECM, and when IL-1 levels are superior to normal, growth factors such as TGF-beta are affected, halting the anabolic phenotype of the chondrocyte.

Although determination of IL-1 is not easy because it is present at picomolar levels, some surrogates are being progressively available, such as imaging techniques with magnetic resonance.

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